REMARKS

Claims 1-13, 15-20, and 22-26 were pending prior to this response. By the present communication, claims 2, 13, 15, 18, and 26 have been cancelled without prejudice, no claims have been added, and claims 1, 10, 16, and 19 have been amended to define Applicants' invention with greater particularity. The claim amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1, 3-12, 16, 17, 19, 20, and 22-25 are currently pending.

The Rejection Under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 1-13, 15-20, and 22-26 under 35 U.S.C. § 112, first paragraph, for allegedly lacking description commensurate with the scope of the claims, as applied to the currently pending claims. Applicants disagree with the Examiner's application of Univ. of Rochester v G.D. Searle & Co., Inc., 358 USPQ2d 1886 (Fed. Cir. 2004) to the present claims. In the Univ. of Rochester case, the Applicants were claiming a compound that interacted with a particular chemical entity, namely PGHS-2. Presumably, a class of compounds having certain structural characteristics in common would be required. By contrast, in the present invention claim 1 describes "a method for identifying a polynucleotide encoding a enzyme of interest", but does not require that the polynucleotide encoding the enzyme of interest have any other property than its ability to hybridize to a probe polynucleotide that has been preselected by the practioner as containing a probe-length portion of a DNA sequence that encodes "an enzyme of interest". The user is free to select "the enzyme of interest," but the target in this case is unknown and cannot be described chemically other than by its hybridization with the probe molecule. Thus there is a fundamental difference between the claims of the Univ. of Rochester case and the claims at issue here.

No description of the atoms making up either the probe molecule or the enzyme of interest needs to be provided or can be provided and Applicants respectfully submit that those of skill in the art would understand that the chemical interaction known in the art as "hybridization" is a specific description of a chemical phenomenon.

Therefore, it appears that the Examiner is interpreting the "written description requirement" as requiring that the claim be narrowed in an inappropriate manner. The invention methods, as defined by amended claim 1, do not require one skilled in the art to arrive at any particular chemical entity that could be described in terms of the atomic makeup or chemical structure. All that is required, is hybridization of a polynucleotide to a complementary segment in a probe bearing a detectable label. Moreover, the "common attribute" that functions in the invention claims is hybridization of complementary DNA sequences, which (under such conditions and for such time as to allow hybridization of complementary sequences, *as required in claim 1*) is a universal chemical phenomenon and not unpredictable, despite the Examiner's assertion to the contrary.

What is "common" and predictable in all DNA hybridization reactions under suitable conditions is that A binds to T and C binds to G, just the same as oxygen binds to hydrogen under suitable conditions. Thus, complementary sequences under the right conditions inevitably bind to one another and the chemical laws governing such a phenomenon do not differ according to whether the DNA sequence from which the probe is constructed encodes one or a different type of enzyme. If an analogy to chemical interactions between specific atoms or combinations is required, Applicants submit that A, T, C and G are specific, commonly known chemical constructs and the binding affinity of complementary strands of DNA is so well known in the art that an Applicant is not required to meet the "heightened" written description requirement of Section 112, first paragraph.

Thus Applicants submit that the Examiner's demand for application of the "heightened" written description requirement appropriate to an unpredictable art area (Office Action, page 6) is inapposite as applied to the present claims. In view of the universal applicability and predictability of the chemistry involved, and the total absence of any *claim* to discovery of a particular chemical construct or particular type of enzymatic activity, applicants respectfully submit that the description of the invention clearly allows persons of ordinary skill in the art to recognize the that [the inventors] invented what is *claimed* as required by *In re Gosteli* (872 F.2d 1008,1012, 10 USPQ2d 1614 (Fed. Cir. 1989).

To further prosecution of this application, Applicants have amended claim 1 to recite "A method for identifying an enzyme of interest, comprising: (a) obtaining a plurality of polynucleotides derived from a mixed population of organisms or more than one organism; (b) normalizing the representation of organisms present in the plurality of polynucleotides to increase representation of rare species; (c) contacting a library containing clones of normalized polynucleotides from (b) with at least one oligonucleotide probe labeled with a detectable molecule, wherein the probe comprises at least a portion of a polynucleotide sequence encoding an enzyme of interest; (d) incubating the clones under such conditions and for such time as to allow hybridization of complementary sequences; (e) separating clones with an analyzer that detects the detectable molecule; (f) contacting the separated clones with a reporter system that comprises a substrate for the enzyme of interest; and (g) identifying clones capable of modulating expression or activity of the reporter system thereby identifying a polynucleotide that encodes the enzyme of interest." The amended language has been narrowed to recite an enzyme, a more clearly described probe, and conditions for identifying clones. Support for the amended claim language may be found in the Specification at page 34, lines 1-5; page 17, lines 14-18 and lines 21-29.

Therefore, Applicants respectfully submit that claim 1 and those dependent thereon, as presently amended, meet the requirements of "written description" under 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claim 22 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

With regard to claim 22, the Examiner alleges that the phrase "small molecule" is a relative term, thus introducing lack of clarity into the claim. However, Applicants submit that the phrase "small molecule" as used in Applicants' specification and claims does not refer specifically to the size of the molecule. Despite the Examiner's assertion that the broadest

dictionary definition of the term "small" should prevail, Applicants submit that such an interpretation is "unreasonable" and thus in contravention of the rules covering definiteness, which hold that a dictionary definition does not necessarily apply when a term is used as a term of art. Applicants submit that those of skill in the art would understand "small" in the phrase "small molecule" as belonging to a term of art that distinguishes, for example, between enzymatic chemical compounds, and enzymatic polypeptides.

Not only is the phrase "small molecule" used as a term of art in the Specification and in claim 22, it would be understood by those of skill in the art to be correctly used. Thus, Applicants disagree with the Examiner's assertion that Applicants "acting as their own lexicographers" have given the term "small" in the phrase "small molecule" a meaning that is "repugnant to the usual meaning of that term" (Office Action, transition from page 8 to page 9). Moreover, Applicants respectfully submit that, because the term "small molecule" has been used in the Specification as a term of art (as is "hybridize" and "hybridization"), there is no requirement for Applicants to provide a detailed explanation of the phrase that distinguishes between the dictionary meaning of the term "small" in a general context, and the meaning of the term when used in a phrase ("small molecule") that is as a term of art. (See the Specification at page 43, lines 4-18; page 45, lines 4-9; page 76, lines 31-32.)

Accordingly, Applicants respectfully submit that those of skill in the art would readily understand the meaning of the phrase "small molecule" as used in claim 22, and respectfully request reconsideration and withdrawal of the rejection of claim 19 under 35 U.S.C. § 112, second paragraph.

The Rejection Under 35 U.S.C. § 102 (e)

Applicants respectfully traverse the rejection of claims 1-10, 13, 15-20 and 22-26 under 35 U.S.C. § 102 (e) as allegedly being anticipated by Thompson et al. (U.S. Patent No. 5,824,485; hereinafter "Thompson"). Claims 2, 13, 15, 18 and 26 have been cancelled without prejudice, thereby rendering the rejection moot as to these claims. Therefore, Applicants will address the rejection as to the currently presented claims.

Applicants respectfully submit that the invention methods for identifying a bioactivity or a biomolecule of interest, as defined by amended claim 1, distinguish over the disclosure of Thompson by requiring:

(a) obtaining a plurality of polynucleotides derived from a mixed population of organisms or more than one organism;

(b) normalizing the representation of organisms present in the plurality of polynucleotides to increase representation of rare species;

(c) contacting a library containing clones of normalized polynucleotides from (b) with at least one oligonucleotide probe labeled with a detectable molecule, wherein the probe comprises at least a portion of a polynucleotide sequence encoding an enzyme of interest;

(d) incubating the clones under such conditions and for such time as to allow hybridization of complementary sequences;

(e) separating clones with an analyzer that detects the detectable molecule;

(f) contacting the separated clones with a reporter system that comprises a substrate for the enzyme of interest; and

(g) identifying clones capable of modulating expression or activity of the reporter system thereby identifying a polynucleotide that encodes the enzyme of interest.

To clarify the meaning of the term "normalizing" as used in claim 1, Applicants have amended the claim to recite "normalizing the representation of organisms present in the plurality of polynucleotides to increase representation of rare species." It is also important to note that the methods of the present invention are directed to the abundance of DNA, not copy number of clones.

Thompson is silent regarding "normalizing" environmental DNA to increase representation of polypeptides of rare species in a library assembled from a sample including a mixed population of organisms, as is required by Applicants' claims. Applicants disagree with the assertion in the office action stating that Thompson discloses "normalizing the plurality of polynucleotides," and citing Thompson col. 32, lines 14-16. Applicants respectfully direct the

Examiner's attention to the sentence in full-context. Thompson states, "More than one initial library may be *pre-screened*, and DNA from *all the positive clones can be pooled* and used for making the biased combinatorial library." (Col. 32, lines 13-16) Thompson goes further to state that, "*Instead of using only the total pooled genomic DNA or cDNA* of the donor organism(s), this approach will *reduce the number of clones that need to be screened* and increase the percentage of clones that will produce compounds of interest. The *preselected* fragments of DNA contain genes encoding partial or complete biosynthetic pathways, and may be *preselected by hybridizing to an initial DNA library* a plurality of probes *prepared from known genes* that may be related to or are involved in producing compounds of interest." (Col. 31, line 65- Col. 32 line 7) Further, Thompson states: "The remaining DNA is thus *biased toward coding regions* that encode proteins involved in secondary metabolism" (Col. 32, lines 54-56) (*Emphasis added*).

As evidence of Thompson's alleged disclosure of normalizing, the Examiner asserts that Thompson is "'equalizing' slow growing members in a mixed population" and repairing damaged DNA to "equalize" the numbers of the damaged polynucleotides in the sample (Office Action, page 17). However, Thompson does not use the term "equalize" in connection with such activities and, in fact, Applicants disagree that such techniques would result in "increasing the representation of rare species in the sample." Thompson's repair of damaged DNA or cloning of uncultured organisms to avoid prejudice to slow growing species would, in both cases, tend to restore the natural distribution of polypeptides of various species in the sample because Thompson does not disclose that only rare polynucleotides would be need to be repaired or would be slow growing. For example, over-represented species are just as likely to have damaged DNA as underrepresented species. In short, Thompson fails to disclose any procedure by which the complexity of the DNA population obtained for the library is analyzed and treated in such a way that representation of species that are rare in the mixed population is increased in the library.

To reduce the number of *clones* that need to be screened, Thompson describes pre-selection of DNA fragments for the screening library using probes and refers to this process as "biasing" a library. Such probes are described as being "prepared from known genes that may be

related to or are involved in producing compounds of interest" (Thompson, Col 32, lines 6-7). However, rather than using the probes for screening (e.g., identifying molecules having a nucleotide sequence complementary to the probes) of a library of already "normalized" naturally occurring DNA molecules, as in Applicants' claim 1, Thompson uses the activity probe concept for pre-screening, pre-selecting and preparing "chimeric" and "biased" *combinatorial expression libraries*" (See Thompson, Section 5.1.6.) prior to screening.

Applicants respectfully submit that the dictionary definition of "normalization" applied by the Examiner as "to cause to conform to a norm or standard" is improperly applied to the claims at issue because "normalization" in the context of the present claims is "a term of art" and those of skill in the art would understand "normalization" as a term of art and not as having the common dictionary meaning applied by the Examiner.

For example, "normalizing" and the advantages of libraries that are "normalized" are described in U.S. Patent 6,174,673 (hereinafter "the '673 patent"), which is incorporated by reference into the present application:

> One embodiment for forming a normalized library from an environmental sample begins with the isolation of nucleic acid from the sample. This nucleic acid can then be fractionated prior to normalization to increase the chances of cloning DNA from minor species from the pool of organisms sampled. DNA can be fractionated using a density centrifugation technique, such as a cesium-chloride gradient. When an intercalating agent, such as bis-benzimide is employed to change the buoyant density of the nucleic acid, gradients will fractionate the DNA based on relative base content. Nucleic acid from multiple organisms can be separated in this manner, and this technique can be used to fractionate complex mixtures of genomes. This can be of particular value when working with complex environmental samples... This "normalization" approach reduces the redundancy of clones from abundant species and increases the representation of clones from rare species. These normalized libraries allow for greater screening efficiency resulting in the identification of cells encoding novel biological catalysts.

The '673 patent, incorporated by reference in the instant application, also teaches: "single-stranded nucleic acid representing an enrichment of rare sequences is amplified using techniques well known in the art, such as polymerase chain reaction (Bames, 1994), and used to

generate gene libraries. This procedure leads to the amplification of rare or low abundance nucleic acid molecules, which are then used to generate a gene library which can be screened for a desired bioactivity."

In further support of the Applicants' arguments regarding "normalization" as a term of art, copies of Soares et al., "Construction and characterization of a normalized cDNA library," Proc. Natl. Acad. Sci. USA, Vol. 91, pp. 9228-9232, September 1994 Biochemistry (Exhibit A, attached hereto) and Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory Press, 1989, pp. 8.6-8.10 (Exhibit B, attached hereto), have been provided for the Examiner's convenience.

In addition, Applicants question the point of the Examiner's statement that the use of "comprising" language in the claims does not limit the "order" in which the method steps are to be carrier out. Applicants respectfully submit that the claim language prescribes normalization of the polynucleotides prior to formation of the library. For example, claim 1 recites: "contacting *a library containing clones of normalized polynucleotides* from (b) with at least one oligonucleotide probe labeled with a detectable molecule, wherein the probe comprises at least a portion of a polynucleotide sequence encoding an enzyme of interest." Thus, the claim language already requires the polynucleotides to be normalized before the library of clones is prepared and "contacted".

In addition, Thompson's omission of a "normalizing step" as the term is understood in the art makes the order of the steps in the claim irrelevant. To establish anticipation under 35 U.S.C. § 102 (e) each and every element of the claimed invention must be disclosed by a single reference. As Thompson fails to disclose each and every element of claim 1 (and claims dependent thereon) as would be required to establish anticipation under 35 U.S.C. 102(b). Therefore, reconsideration and withdrawal of the rejection over Thompson are respectfully requested.

The Rejection under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Applicants respectfully traverse the rejection of claims 1-10, 13, 15-20, and 22-26 under 35 U.S.C. § 103 as allegedly being unpatentable over Thompson (as above) and Miao et al, Biotechnology and Bioengineering (1993) 42:708-715, hereinafter "Miao". Claims 2, 13, 15, 18 and 26 have been cancelled without prejudice, thereby rendering the rejection moot as to these claims. Therefore, Applicants will address the rejection as to the currently presented claims.

Applicants respectfully submit that the invention methods for identifying a bioactivity or a biomolecule of interest, as defined by amended claim 1, distinguish over the combined disclosures of Thompson and Miao by requiring:

(a) obtaining a plurality of polynucleotides derived from a mixed population of organisms or more than one organism;

(b) normalizing the representation of organisms present in the plurality of polynucleotides to increase representation of rare species;

(c) contacting a library containing clones of normalized polynucleotides from (b) with at least one oligonucleotide probe labeled with a detectable molecule, wherein the probe comprises at least a portion of a polynucleotide sequence encoding an enzyme of

interest;

(d) incubating the clones under such conditions and for such time as to allow hybridization of complementary sequences;

(e) separating clones with an analyzer that detects the detectable molecule;

(f) contacting the separated clones with a reporter system that comprises a substrate for the enzyme of interest; and

(g) identifying clones capable of modulating expression or activity of the reporter system thereby identifying a polynucleotide that encodes the enzyme of interest.

Thus, the discussion above regarding the deficiencies of Thompson apply equally and are incorporated here. In addition Applicants submit that Thompson fails to suggest the invention methods, as recited by amended claim 1, because Thompson fails to disclose or suggest normalizing the polynucleotides obtained from the mixed population to increase the representation of rare species prior to placement of the polynucleotides into clones and formation of the library to increase the chances of discovering an enzyme from an organism whose presence in the original sample is rare. Instead Thompson discusses repair of damaged DNA and methods for avoiding bias to slow growing members in a mixed population, either of which may as easily restore the original distribution of organisms in the sample as not, as Applicants have discussed above. Therefore, Applicants also respectfully submit that Thompson would not motivate those of skill in the art to modify Thompson to arrive at the presently presented invention methods because Thompson's comments regarding preparation of "activity biased" libraries would not motivate those of skill in the art to normalize the library by increasing the representation of rare organisms so that chances of discovering an activity produced by a rare organism are increased. Indeed, Thompson's activity biasing of the library may well increase the chances that screening *will not* yield an enzyme, or other activity, produced by a rare organism because the commonest species in the sample may be selected by the activity probe and therefore have increased overrepresentation in Thompson's "biased" screening library as compared with the sample.

Applicants submit that the disclosure of Miao fails to remedy the deficiencies of Thompson under 35 U.S.C. § 103. Miao's disclosure pertains to use of C12FDG as a fluorescent substrate in FACS screening of single bacterial cells of one species (i.e., E. coli). Thus, like Thompson, Miao is completely silent regarding screening of a *normalized* library prepared by treating the polynucleotides obtained from a mixed population to increase the representations of species that were rare in the original sample. Indeed, since Miao's disclosure does not pertain to screening of a plurality of species at all, as would be inherent in a "mixed population", Applicants submit that the combined disclosures of Thompson and Miao would be insufficient to motivate those of skill in the art to modify Thompson so as to yield the present invention.

In addition, even if those of skill in the art were motivated by the combined disclosures of Thompson and Miao to arrive at the invention methods, Applicants submit that the cited art would fail to provide the reasonable expectation of success that is required to show unpatentability under 35 U.S.C. § 103. Because both Thompson and Miao fail to discuss any technique by which a diverse library can be adjusted to increase the representation of polynucleotides obtained from rare members, those of skill in the art would not be justified in assuming success in the outcome of any technique that might be devised.

Accordingly, Applicants respectfully submit that the combined disclosures of Thompson and Miao, including Miao's disclosure regarding rapid screening using C12FDG, are not sufficient to teach or suggest the invention methods of amended claim 1. Thus, Applicants respectfully submit that the pending claims are not *prima facie* obvious over Thompson, or the combined disclosures of Thompson and Miao. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

In summary, in view of the amendments and for the reasons set forth herein, Applicants respectfully submit that claims 1, 3-12, 16, 17, 19, 20, and 22-25 clearly and patentably define the invention and allowance of the claims is respectfully requested. If the Examiner would like to discuss any issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Exhibit A
Exhibit B